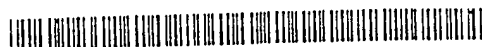


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(54) Title: RECEPTOR SELECTIVE CANNABIMIMETIC AMINOALKYLINDOLES

(57) Abstract: Disclosed are cannabimimetic aminoalkylindole compounds and methods for their manufacture. The disclosed com-
pounds are surprisingly potent and selective cannabinoids. Also disclosed are methods of using the disclosed compounds, including
use of the disclosed compounds to stimulate a cannabinoid receptor, to provide a physiological effect in an animal or individual and
to treat a condition in an animal or individual.

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RECEPTOR SELECTIVE CANNABIMIMETIC AMINOALKYLINDOLES

Field of the Invention

The present invention relates generally to indole compounds exhibiting
5 cannabimimetic activity. The present invention is more particularly concerned with
new and improved aminoalkylindole compounds exhibiting high binding affinity for
at least one cannabinoid receptor and/or high selectivity for one cannabinoid
receptor, pharmaceutical preparations employing these compounds and methods of
administering therapeutically effective amounts of these compounds to provide a
10 physiological effect.

Background of the Invention

Classical cannabinoids such as the marijuana derived cannabinoid
 Δ^9 -tetrahydrocannabinol, (Δ^9 -THC) produce their pharmacological effects through
15 interaction with specific cannabinoid receptors in the body. So far, two
cannabinoid receptors have been characterized: CB1, a central receptor found in the
mammalian brain and peripheral tissues and CB2, a peripheral receptor found only
in the peripheral tissues. Compounds that are agonists or antagonists for one or
both of these receptors have been shown to provide a variety of pharmacological
20 effects.

There is considerable interest in developing cannabimimetic compounds
possessing high affinity for one of the CB1 or CB2 receptors. Such compounds
may offer a rational therapeutic approach to a variety of disease conditions. One
class of cannabimimetic compound encompasses indole derivatives such as the
25 well-known aminoalkylindoles represented by WIN 55212-2 {(R)-(+)-[2,3-dihydro-5-
methyl-3-[(4-morpholinyl)methyl]-pyrrolo[1,2,3-*de*]-1,4-benzoxazin-6-yl](1-naptha-
lenyl)methanone}. Aminoalkylindoles of this type typically have a carbon linked
alkylheterocyclic substituent at the indole-1 position, which is believed to be
important for their cannabimimetic activities. These known materials are not
30 selective for preferential activation of one of the CB1 or CB2 receptors.

substituents each independently selected from amino, halogen, hydroxy, nitro, nitroso, azido, isothiocyanato, cyano, COOH, CONR³R⁴ where R³ and R⁴ each independently comprise H, alkyl or substituted alkyl, NCOR³R⁴ where R³ and R⁴ each independently comprise H, alkyl, substituted alkyl, CF₃, SO₂NR³R⁴ where R³ and R⁴ each independently comprise H, alkyl, substituted alkyl or CF₃; or a salt of any of the above.

In one preferred aspect of the invention the novel compounds can be represented by structural formula I above, wherein:

10 wherein:

Z comprises hydrogen;

Alk comprises a C₁₋₂alkyl group;

X comprises a 5, 6 or 7 member heterocyclic ring, including at least one heteroatom independently selected from oxygen, nitrogen and sulfur; a substituted 5, 6 or 7 member heterocyclic ring, including at least one heteroatom independently selected from oxygen, nitrogen and sulfur; a bicyclic ring; or a bicyclic ring including at least one heteroatom independently selected from oxygen, nitrogen and sulfur;

R comprises hydrogen;

20 Y comprises carbonyl; and

Ar comprises adamantyl; azoadamantyl; phenyl; naphthyl; 9-anthracenyl; pyridinyl; quinolinyl; isoquinolinyl; quinazolinyl; an aliphatic bicyclic ring; an azabicyclic ring; any of the above with no more than two substituents each independently selected from amino, halogen, hydroxy, nitro, nitroso, azido, isothiocyanato, cyano, COOH, CONR³R⁴ where R³ and R⁴ each independently comprise H, alkyl or substituted alkyl, NCOR³R⁴ where R³ and R⁴ each independently comprise H, alkyl, substituted alkyl, CF₃, SO₂NR³R⁴ where R³ and R⁴ each independently comprise H, alkyl, substituted alkyl or CF₃; or a salt of any of the above.

30

otherwise specifically defined, "alkylmercapto" refers to the general formula -S-alkyl. Unless otherwise specifically defined, "alkylamino" refers to the general formula -(NH)-alkyl. Unless otherwise specifically defined, "di-alkylamino" refers to the general formula -N-(alkyl)₂. Unless otherwise specifically defined, an aromatic ring is an unsaturated ring structure, substituted or unsubstituted, that includes only carbon as ring atoms. Unless otherwise specifically defined, a heteroaromatic ring is an unsaturated ring structure, substituted or unsubstituted, that has carbon atoms and one or more heteroatoms, including oxygen, nitrogen and/or sulfur, as ring atoms, for example, pyridine, furan, quinoline, and their derivatives. Unless otherwise specifically defined, a carbocyclic ring is a saturated ring structure, substituted or unsubstituted, that includes only carbon as ring atoms, for example, cyclohexane. Unless otherwise specifically defined, a heterocyclic ring is a saturated ring structure, substituted or unsubstituted, that has carbon atoms and one or more heteroatoms, including oxygen, nitrogen and/or sulfur, as ring atoms, for example, piperidine, morpholine, piperazine, and their derivatives. Unless otherwise specifically defined, an aliphatic bicyclic ring is a polycyclic structure, substituted or unsubstituted, having about 6 to about 12 ring atoms that includes only carbon as ring atoms, for example bicyclohexane and bicyclodecane. Unless otherwise specifically defined, a heterobicyclic ring is a polycyclic structure, substituted or unsubstituted, having about 6 to about 12 ring atoms that has carbon atoms and one or more heteroatoms, including oxygen, nitrogen and/or sulfur, as ring atoms, for example tropane.

Substituent groups useful in the invention are those groups that do not significantly diminish the biological activity of the inventive compound. Unless otherwise specifically defined, substituent groups that do not significantly diminish the biological activity of the inventive compound include, for example, alkyl, substituted alkyl, phenyl, substituted phenyl, OH, NH₂, alkoxy, halogen, CF₃, CN, NCS, azido, CONR³R⁴ where R³ and R⁴ each independently comprise H, alkyl or substituted alkyl, NCOR³R⁴ where R³ and R⁴ each independently comprise H, alkyl, substituted alkyl, CF₃, SO₂NR³R⁴ where R³ and R⁴ each independently comprise H, alkyl, substituted alkyl or CF₃, sulfonamide, or lower alcohol.

compounds to oppose initiation of an agonistic response from a cannabinoid receptor.

The inventive cannabinoid compounds described herein, and physiologically acceptable salts thereof, have pharmacological properties when administered in therapeutically effective amounts for providing a physiological response in individuals and/or animals. Thus, another aspect of the invention is the administration of a therapeutically effective amount of at least one of the inventive cannabimimetic compounds, or a physiologically acceptable salt thereof, to an individual or animal to provide a physiological response.

Additionally, some of the halogen containing analogs, for example those analogs comprising iodide and fluoride, are potential radioactive probes for imaging *in vivo* the distribution of cannabinoid receptors.

A better understanding of the invention will be obtained from the following detailed description of the article and the desired features, properties, characteristics, and the relation of the elements as well as the process steps, one with respect to each of the others, as set forth and exemplified in the description and illustrative embodiments.

Description of a Preferred Embodiment

As used herein, a "therapeutically effective amount" of a compound, is the quantity of a compound which, when administered to an individual or animal, results in a sufficiently high level of that compound in the individual or animal to cause a discernible increase or decrease in stimulation of cannabinoid receptors.

Such discernible increase or decrease in stimulation of cannabinoid receptors can provide a physiological effect in the individual or animal.

Physiological effects that result from CB1 cannabinoid receptor interaction with agonist compounds include relief of pain, peripheral pain, neuropathic pain, glaucoma, epilepsy and nausea such as associated with cancer chemotherapy; appetite enhancement; selective killing of glioma and breast cancer cells; alleviation of the symptoms of neurodegenerative diseases including Multiple Sclerosis, Parkinson's Disease, Huntington's Chorea and Alzheimer's Disease, reduction of

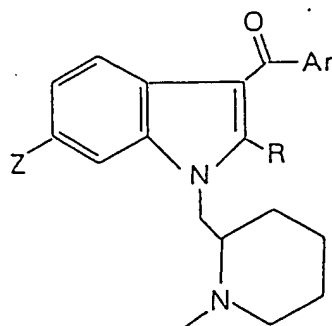
example, saline, sterile water, Ringer's solution, and isotonic sodium chloride solutions. The specific dosage level of compound will depend upon a number of factors, including, for example, biological activity of the particular preparation, age, body weight, sex and general health of the individual being treated.

5 The following examples are given for purposes of illustration only in order that the present invention may be more fully understood. These examples are not intended to limit in any way the scope of the invention unless otherwise specifically indicated.

10 The prepared cannabimimetic indole derivatives can generally be described with reference to exemplary structural formulas 1 and 2 below.

The inventive compounds of exemplary structural formula 1 include both racemics and two enantiomers and are listed in TABLE 1.

15 exemplary structural formula 1



20 It should be noted that alk-X for all of the materials of TABLE 1 was 1-(N-methyl-2-piperidinyl)methyl.

TABLE 1					
analog	Z	R	Ar	K _i nM	
				CB1	CB2
2-7(R,S)	H	H	2-iodo-5-nitrophenyl	403	5.7
2-7(R)	H	H	2-iodo-5-nitrophenyl	285	0.53
2-7(S)	H	H	2-iodo-5-nitrophenyl	906	9.5

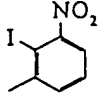
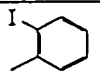
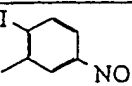
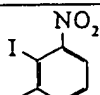
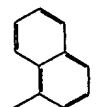
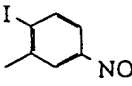
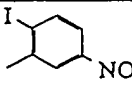
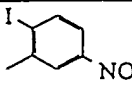
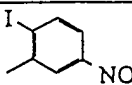
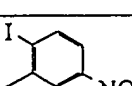
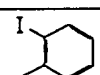
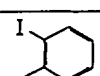
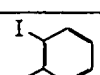
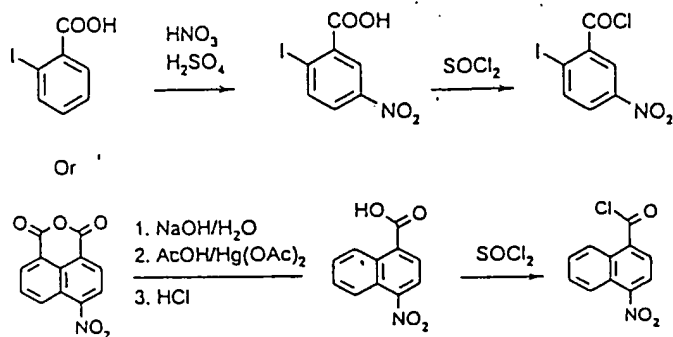
TABLE 2							
						Ki nM	
analog	Z	R	R ¹	R ²	Ar	CB1	CB2
2-27	H	H	O	CH ₂ Ph		2383	927.5
2-28	H	H	O	CH ₃		27.93	226.3
2-29	H	H	O	CH ₃		848.1	48.45
2-30	H	H	O	CH ₃		464.3	153.5
2-31	H	H	O	CH ₃		5.696	26.56
2-32(R,S)	H	H	CH ₂	CH ₃		239.4 (R,S)	3.411 (R,S)
2-32(R)	H	H	CH ₂	CH ₃		139.7 (R)	1.416 (R)
2-32(S)	H	H	CH ₂	CH ₃		2029 (S)	160.5 (S)
2-32(R,S) human	H	H	CH ₂	CH ₃			13.60 (R,S), Human
2-32(R) human	H	H	CH ₂	CH ₃			6.688 (R), Human
2-33	H	H	CH ₂	CH ₃	1-Adamantyl	11.93	4.804
2-33 human	H	H	CH ₂	CH ₃	1-Adamantyl		2.321 Human
2-34(R,S)	H	H	CH ₂	CH ₃		2.889 (R,S)	3.345 (R,S)
2-34(R)	H	H	CH ₂	CH ₃		1.573 (R)	1.558 (R)
2-34(S)	H	H	CH ₂	CH ₃		14.17 (S)	6.789 (S)

TABLE 2							
						Ki nM	
analog	Z	R	R ¹	R ²	Ar	CB1	CB2
2-48	H	H	CH ₂	CH ₃		390.0	47.17
2-49	H	H	CH ₂	CH ₃		29.07	18.63
2-50	H	H	CH ₂	CH ₃			
2-51	H	H	CH ₂	CH ₃			
2-52	H	H	CH ₂	CH ₃			
2-53	H	H	CH ₂	CH ₃			

Preparation of compounds:

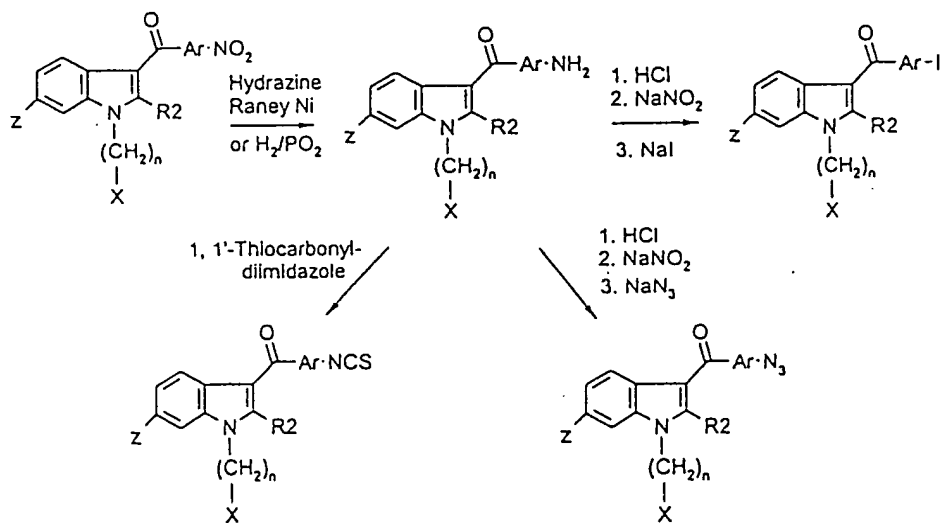
- 5 The above materials were generally prepared following Scheme 1 with the exception that N-methyl-2-piperidinemethyl chloride is used in place of acetoxylalkylhalides for the alkylation of the indole 1-position.

Scheme 3



After these acid chlorides are connected at the indole 3-position, the nitro group therein can be further transformed into amino, iodo, azido, and isothiocyanate groups according to the methods outlined in Scheme 4.

Scheme 4



Examples of specific analogs were prepared as follows:

10 1-(N-Methyl-2-piperidiny)methyl-3-(3-quinolinecarbonyl)-1H-indole.

To the suspension of 200 mg (1.5 mmol) of anhydrous AlCl_3 in 8 ml absolute methylene chloride was added 287.4 mg (1.5 mmol) 3-quinolinecarbonyl chloride in 5 ml methylene chloride and the reaction mixture was stirred 30 min at room 22-

general preparation and specific preparation examples would know how to modify the disclosed procedures to achieve the above listed analogs.

The prepared cannabinoid compounds were tested for CB2 receptor binding affinity and for CB1 receptor affinity (to determine selectivity for the CB2 receptor).

5 As used herein, "binding affinity" is represented by the IC_{50} value which is the concentration of an analog required to occupy the 50% of the total number (B_{max}) of the receptors. The lower the IC_{50} value, the higher the binding affinity. As used herein a compound is said to have "binding selectivity" if it has higher binding affinity for one receptor compared to the other receptor; e.g. a compound that has
10 an IC_{50} of 0.1 nM for CB1 and 10 nM for CB2, is 100 times more selective for the CB1 receptor. The binding affinities (K_i) are expressed in nanomoles (nM).

For the CB1 receptor binding studies, membranes were prepared from rat forebrain membranes according to the procedure of P.R. Dodd et al; A Rapid Method for Preparing Synaptosomes: Comparison with Alternative Procedures,
15 Brain Res., 107 - 118 (1981). The binding of the novel analogues to the CB1 cannabinoid receptor was assessed as described in W.A. Devane et al; Determination and Characterization of a Cannabinoid Receptor in a Rat Brain, Mol. Pharmacol., 34, 605 - 613 (1988) and A. Charalambous et al; "5'-azido ⁸-THC: A Novel Photoaffinity Label for the Cannabinoid Receptor", J. Med. Chem., 35,
20 3076 - 3079 (1992) with the following changes. The above articles are incorporated by reference herein.

Membranes, previously frozen at -80 °C, were thawed on ice. To the stirred suspension was added three volumes of TME (25mM Tris-HCl buffer, 5 mM $MgCl_2$ and 1 mM EDTA) at a pH 7.4. The suspension was incubated at 4 °C for 30 min.
25 At the end of the incubation, the membranes were pelleted and washed three times with TME.

The treated membranes were subsequently used in the binding assay described below. Approximately 30 µg of membranes were incubated in silanized 96-well microtiter plate with TME containing 0.1 % essentially fatty acid-free bovine
30 serum albumin (BSA), 0.8 nM [³H] CP-55,940, and various concentrations of test materials at 30 °C for 1 hour. The samples were immediately filtered using a

imaging *in vivo* the distribution of cannabinoid receptors. Further, azido containing compounds would be useful as affinity probes for characterizing binding pockets of cannabinoid receptors.

While preferred embodiments of the foregoing invention have been set forth
5 for purposes of illustration, the foregoing description should not be deemed a limitation of the invention herein. Accordingly, various modifications, adaptations and alternatives may occur to one skilled in the art without departing from the spirit and scope of the present invention.

any of the above.

2. The compound of claim 1, wherein:

Z comprises hydrogen;

Alk comprises a C₁₋₂alkyl group;

X comprises a 5, 6 or 7 member heterocyclic ring, including at least one heteroatom independently selected from oxygen, nitrogen and sulfur; a substituted 5, 6 or 7 member heterocyclic ring, including at least one heteroatom independently selected from oxygen, nitrogen and sulfur; a bicyclic ring; or a bicyclic ring including at least one heteroatom independently selected from oxygen, nitrogen and sulfur;

R comprises hydrogen;

Y comprises carbonyl; and

Ar comprises adamantyl; azoadamantyl; phenyl; naphthyl; 9-anthracenyl; pyridinyl; quinolinyl; isoquinolinyl; quinazolinyl; an aliphatic bicyclic ring; an azabicyclic ring; a heterobicyclic ring; any of the above with no more than two substituents each independently selected from amino, halogen, hydroxy, nitro, nitroso, azido, isothiocyanato, cyano, COOH, CONR³R⁴ where R³ and R⁴ each independently comprise H, alkyl or substituted alkyl, NCOR³R⁴ where R³ and R⁴ each independently comprise H, alkyl, substituted alkyl, CF₃, NSO₂R³R⁴ where R³ and R⁴ each independently comprise H, alkyl, substituted alkyl or CF₃; or a salt of any of the above.

3. The compound of claim 1, wherein:

Z is H;

R is H; and

Ar is 2-iodo-5-nitrophenyl.

4. The compound of claim 1, wherein:

Z is H;

R is H; and

7. The compound of claim 5, wherein:

Z is H;

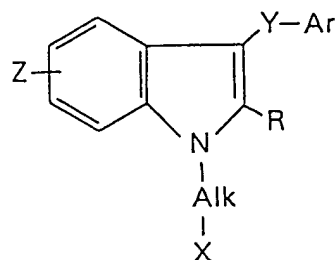
R is H;

R¹ is CH₃;

R² is H; and

Ar is 2-iodophenyl.

8. A pharmaceutical preparation comprising a therapeutically effective amount of a compound of the formula below, including physiologically acceptable salts, diastereomers, enantiomers, double bond isomers or mixtures thereof:



wherein:

Z comprises at least one substituent independently chosen from hydrogen; halogen; hydroxy; alkoxy; thioalkoxy; aryl and lower alkyl;

Alk comprises an alkyl group or a substituted alkyl group;

X comprises a 5, 6 or 7 member heterocyclic ring, including at least one heteroatom independently selected from oxygen, nitrogen and sulfur; a substituted 5, 6 or 7 member heterocyclic ring, including at least one heteroatom independently selected from oxygen, nitrogen and sulfur; a bicyclic ring; or a bicyclic ring including at least one heteroatom independently selected from oxygen, nitrogen and sulfur;

R comprises hydrogen, CN, CHO, an alkyl group or a substituted alkyl group;

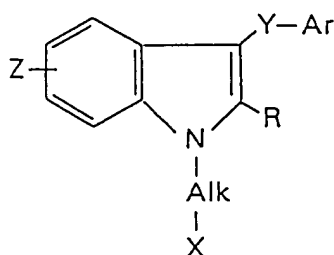
Y comprises carbonyl, CH=CH (cis or trans), CONH or C=NH; and

Ar comprises adamantyl; azoadamantyl; phenyl; naphthyl; 9-anthracenyl;

Y comprises carbonyl, CH=CH (cis or trans), CONH or C=NH; and

Ar comprises adamantyl; azoadamantyl; phenyl; naphthyl; 9-anthracenyl; pyridinyl; quinolinyl; isoquinolinyl; quinazolinyl; an aliphatic bicyclic ring; an azabicyclic ring; a heterobicyclic ring; any of the above with no more than two substituents each independently selected from amino, halogen, hydroxy, nitro, nitroso, azido, isothiocyanato, cyano, COOH, CONR³R⁴ where R³ and R⁴ each independently comprise H, alkyl or substituted alkyl, NCOR³R⁴ where R³ and R⁴ each independently comprise H, alkyl, substituted alkyl, CF₃, NSO₂R³R⁴ where R³ and R⁴ each independently comprise H, alkyl, substituted alkyl or CF₃; or a salt of any of the above.

10. A method of selectively stimulating a CB2 cannabinoid receptor in an individual or animal comprising administering to the individual or animal a therapeutically effective amount of a compound of the formula below, including physiologically acceptable salts, diastereomers, enantiomers, double bond isomers or mixtures thereof:



wherein:

Z comprises at least one substituent independently chosen from hydrogen; halogen; hydroxy; alkoxy; thioalkoxy; aryl and lower alkyl;

Alk comprises an alkyl group or a substituted alkyl group;

X comprises a 5, 6 or 7 member heterocyclic ring, including at least one heteroatom independently selected from oxygen, nitrogen and sulfur; a substituted 5, 6 or 7 member heterocyclic ring, including at least one heteroatom independently selected from oxygen, nitrogen and sulfur; a bicyclic ring; or a bicyclic ring including at least one heteroatom independently selected

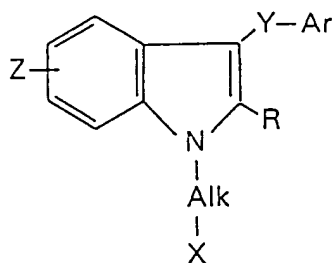
heteroatom independently selected from oxygen, nitrogen and sulfur; a bicyclic ring; or a bicyclic ring including at least one heteroatom independently selected from oxygen, nitrogen and sulfur;

R comprises hydrogen, CN, CHO, an alkyl group or a substituted alkyl group;

Y comprises carbonyl, CH=CH (cis or trans), CONH or C=NH; and

Ar comprises adamantyl; azoadamantyl; phenyl; naphthyl; 9-anthracenyl; pyridinyl; quinolinyl; isoquinolinyl; quinazolinyl; an aliphatic bicyclic ring; an azabicyclic ring; a heterobicyclic ring; any of the above with no more than two substituents each independently selected from amino, halogen, hydroxy, nitro, nitroso, azido, isothiocyanato, cyano, COOH, CONR³R⁴ where R³ and R⁴ each independently comprise H, alkyl or substituted alkyl, NCOR³R⁴ where R³ and R⁴ each independently comprise H, alkyl, substituted alkyl, CF₃, NSO₂R³R⁴ where R³ and R⁴ each independently comprise H, alkyl, substituted alkyl or CF₃; or a salt of any of the above.

12. A method of treating a condition in an animal or individual comprising administering to the individual or animal in need of such treatment an amount of a compound of the formula below, including physiologically acceptable salts, diastereomers, enantiomers, double bond isomers or mixtures thereof:



wherein:

Z comprises at least one substituent independently chosen from hydrogen; halogen; hydroxy; alkoxy; thioalkoxy; aryl and lower alkyl;

Alk comprises an alkyl group or a substituted alkyl group;

Z comprises at least one substituent independently chosen from hydrogen; halogen; hydroxy; alkoxy; thioalkoxy; aryl and lower alkyl;

Alk comprises an alkyl group or a substituted alkyl group;

X comprises a 5, 6 or 7 member heterocyclic ring, including at least one heteroatom independently selected from oxygen, nitrogen and sulfur; a substituted 5, 6 or 7 member heterocyclic ring, including at least one heteroatom independently selected from oxygen, nitrogen and sulfur; a bicyclic ring; or a bicyclic ring including at least one heteroatom independently selected from oxygen, nitrogen and sulfur;

R comprises hydrogen, CN, CHO, an alkyl group or a substituted alkyl group;

Y comprises carbonyl, CH=CH (cis or trans), CONH or C=NH; and

Ar comprises adamantyl; azoadamantyl; phenyl; naphthyl; 9-anthracenyl; pyridinyl; quinolinyl; isoquinolinyl; quinazolinyl; an aliphatic bicyclic ring; an azabicyclic ring; a heterobicyclic ring; any of the above with no more than two substituents each independently selected from amino, halogen, hydroxy, nitro, nitroso, azido, isothiocyanato, cyano, COOH, CONR³R⁴ where R³ and R⁴ each independently comprise H, alkyl or substituted alkyl, NCOR³R⁴ where R³ and R⁴ each independently comprise H, alkyl, substituted alkyl, CF₃, NSO₂R³R⁴ where R³ and R⁴ each independently comprise H, alkyl, substituted alkyl or CF₃; or a salt of any of the above.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/02501

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/4439, 31/4709, 31/472, 31/496, 31/498, 31/5377; C07D 401/06, 401/14; 413/06
US CL : 514/235.2, 255, 311, 323; 544/143, 355, 546/176, 201

According to International Patent Classification (IPC) or to both national classification and IPC

D. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/235.2, 255, 311, 323; 544/143, 355, 546/176, 201

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US, 6013,648 A (RINALDI et al) 11 January 2000 (11.01.2000), entire document.	1, 2, 8-13
X	US 4,885,295 A (BELL et al) 05 December 1989 (05.12.1989), entire document.	1,2,8, 11-13
X	EISSENSTAT et al. Aminoalkylindoles: Structure-Activity Relationships of Novel Cannabinoid Mimetics. J. Med. Chem. 1995, Vol. 38, No. 16, pages 3094-3105, entire document.	1, 2, 9

☐ Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:

-A- document defining the general state of the art which is not considered to be of particular relevance

-E- earlier application or patent published on or after the international filing date

-L- document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

-O- document referring to an oral disclosure, use, exhibition or other means

-P- document published prior to the international filing date but later than the priority date claimed

-T-

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

-X-

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

-Y-

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

-Z-

document member of the same patent family

Date of the actual completion of the international search

20 April 2002 (20.04.2002)

Date of mailing of the international search report

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Name and mailing address of the ISA/US

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